

Creutzfeldt-Jakob Disease

Summary

Recent media attention on the “Mad Cow” scare in the US has reminded public health of the importance of timely, accurate, surveillance of Creutzfeldt-Jakob disease in Utah and the US. Cases are rare, with a worldwide incidence of approximately 1 per million. Utah averages 1.5 cases of CJD per year, which is similar in incidence to rates reported in the US. Identification and reporting of cases is critical to detect any increases in the occurrence of CJD. Knowledge is key.

Background

Creutzfeldt-Jakob Disease (CJD) is a rare neurodegenerative disorder affecting approximately one in every million persons¹. It is one of several transmissible spongiform encephalopathies (TSE), which occur in varying forms in both humans and animal species. Human TSEs occur in sporadic, familial and acquired forms. No proven treatment exists and cases are always fatal. In addition to CJD, human TSEs include Kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI) and variant Creutzfeldt-Jakob disease (vCJD).

Research supports the prion as the causative agent in TSEs, as detailed in the protein-only hypothesis described by Dr. Stanley B. Prusiner². This hypothesis proposes that the infectious agent, PrP^{Sc}, is a protease-resistant protein devoid of nucleic acid. This protein is an abnormal conformation of a normal host-encoded glycoprotein, PrP^C, found on the surface of a variety of cell types, in particular, neurons. The prion protein gene is highly conserved among mammals suggesting its function to be of some importance³. Evidence suggests that it may play a role in cell adhesion and signaling³.

The secondary structure of PrP^C protein is largely composed of α -helices. The pathogenicity of PrP^{Sc}, which is composed of primarily β -sheets, occurs due to its ability to “recruit” normal protein, initiating a conformational conversion into the protein’s pathogenic form². A self-perpetuating cycle is initiated and results in an accumulation of PrP^{Sc} in the brain. Over time, this leads to neuronal loss, gliosis and the characteristic spongiform changes.

Creutzfeldt-Jakob Disease (CJD) is the most common of the human TSEs. Dr. Creutzfeldt and Dr. Jakob, two German neurologists, were the first to describe the disease in the 1920s. CJD is primarily a disease of increasing age, with a median age at death of 68 years¹. As is characteristic with TSEs, it has a relatively long incubation period before the development of symptoms, up to more than 25 years. There are three types of CJD, sporadic, familial or genetic, and iatrogenic. Approximately 85% of all CJD cases are sporadic. The exact cause of sporadic CJD is unclear. Predominant thinking suggests cases occur due to a spontaneous gene mutation in the prion protein gene. Familial or genetic CJD make up between 10 and 15 percent of CJD cases and are a result of an autosomal dominant mutation⁴. Cases of iatrogenic CJD are rare, less than one percent of reported cases. They are primarily a result of neurosurgery with prion-contaminated

instruments, such as EEG depth electrodes, human dura mater grafts, corneal implants or human cadaveric growth hormone (hGH), from PrP^{Sc} infected donors⁴.

CJD can have variations in typical presentation. Often, it is preceded by a constellation of non-specific symptoms including headache, sleep and appetite disturbances and depression⁴. Clinical Hallmarks include rapidly progressive dementia, myoclonic jerks and cognitive impairment. Symptoms usually expand to include one or more of the following; behavior abnormalities, cerebellar dysfunction, ataxia, memory loss, changes in vision, language impairment and both pyramidal and extrapyramidal signs. The course of illness is brief. Median duration of illness is four months and 65% of cases usually die within six months. **See attachments for CDC and WHO case definitions and diagnostic criteria.**

vCJD and “MAD COW” disease

Variant Creutzfeldt-Jakob Disease (vCJD) was first identified in 1996 in the United Kingdom. The UK's National CJD surveillance unit was established in 1990 as a precautionary response to the epizootic of bovine spongiform encephalopathy (BSE). By that point, BSE had affected thousands of herds throughout the U.K since its identification in 1986. It was now feared that the agent responsible for BSE might be transmissible to humans. BSE is believed to have originated from scrapie (a TSE endemic in sheep for centuries, and the disease for which the designation PrP^{Sc} comes from) found in meat and bone meal used as protein supplements for cattle⁵. A change in the rendering process of ruminant protein is hypothesized to have allowed prion-infected material to survive. A unique characteristic of the rogue protein is that it is insoluble and highly resistant to conventional sterilization and disinfection techniques. This change in processing resulted in PrP^{Sc} contaminated cattle feed supplements, initiating the “Mad Cow” epidemic⁵. The National CJD Surveillance unit was established to provide intense monitoring of the epidemiology of CJD, in an effort to identify possible deviations in human TSEs that may occur as a result of consumption of BSE infected cattle and or cattle products.

Five years later, the CJD surveillance unit was notified of three apparent cases of CJD among young people (16, 19, and 29 year old). By the end of 1996, 29 cases of this unusual presentation of CJD had been identified in the UK. Upon further investigation, marked differences in both clinical presentation and neuropathological features between these patients and those with classic CJD became apparent. Differences included young age at onset (median 28 years), early psychiatric symptoms, prominent ataxia, comparatively prolonged illness (median duration of illness of 14 months, ranging from 6 to 40 months), and absence of the typical EEG findings in sporadic CJD⁶. Further, the neuropathology of vCJD revealed unusual florid or “daisy” prion protein plaques (often referred to as Kuru-like plaques) in which an amyloid core is surrounded by “petals” of spongiform change, a feature not seen in classic CJD⁶.

As of December 2003, 145 definite and probable (without neuropathological confirmation) cases of vCJD had been identified in the UK. Additionally, six cases of vCJD have been identified in France and one each in Ireland, Canada and the US⁷. Each of the latter three cases had previously resided in the UK⁴. It unknown whether cases of vCJD are tapering

down or if the epidemic has just begun. Mathematical modeling, based on various assumptions, exists to support both scenarios⁵.

Convincing evidence supports the link between BSE-infected cattle and human cases of vCJD^{8,9,10}. Although prions have never reproducibly been identified in muscle meat, practices have been identified that could inadvertently result in contamination of muscle meat with neuronal tissue. The UK, along with several other countries, including more recently the US, have taken steps to eliminate such practices. Further, since 1989, the US has had in place import controls on any cattle and or most cattle products from any country that has had a positive case of BSE.

Until December 2003, BSE was not known to exist in the US. On December 25th 2003 histopathology and immunohistochemical testing confirmed a diagnosis of BSE in a “downer” cow in Washington State. An ongoing USDA investigation has traced the cow back to herd on a farm in Alberta Canada. All products produced from the cow and produced on the day that the infected cow was processed have been recalled. Additional animals from the source heard were also identified and depopulated. Information pertaining to the ongoing investigation is available online at <http://www.aphis.usda.gov/lpa/issues/bse/bse.html>

CHRONIC WASTING DISEASE

Chronic Wasting Diseases (CWD) is a TSE that occurs in a few North American free-ranging and captive cervid species, namely Elk, mule deer and white tailed deer. CWD is more closely related to scrapie in sheep than it is to BSE. A host of clinical signs are characteristic of CWD and include the loss of fear of humans, ataxia, marked weakness, dehydration, excessive salivation, drooping head and ears and severe emaciation¹¹. As with other TSEs there is a prolonged incubation period, at least one to three years and once clinical signs become apparent, duration of illness is brief – weeks to months. Exact routes of transmission are unknown at this time, though evidence supports both horizontal and indirect (through contact with a contaminated environment) routes. Excreta, placental tissues, and neuronal tissues have been shown to contain varying concentrations of the rogue protein making them infectious and capable of transmitting CWD. Environmental contamination is believed to be the source of infection of disease in several captive herds of deer and elk¹².

The prevalence of CWD is varies widely among biologically or geographically segregated subpopulations, although prevalence is highest in endemic areas of Colorado and Wyoming¹¹. In 2003 eight of the 3,167 samples collected tested positive for CWD from deer and elk in Utah. The disease appears to be centered in the LaSal Mountains east of Moab and Diamond Mountain north of Vernal¹³. The Utah Division of Wildlife does not believe CWD to be widespread in the State at this point.

The World Health Organization (WHO) has stated: “There is currently no evidence that CWD in cervidae (deer and elk) is transmitted to humans.” A recent investigation found no association between consuming large quantities of wild game meat and the development of CJD¹⁴. However, the number of cases developing fatal neurodegenerative disorders

and a history of consuming game meat are small limiting the power to demonstrate causality between CWD and human illness. The possibility of transmission of CWD to humans, and the scenarios similarity to what has occurred with BSE and vCJD, reemphasizes the need to be vigilant in accurately diagnosing and providing ongoing active surveillance to be able to closely monitor trends of human illness in Utah and the US.

CJD in Utah

CJD was added to Utah's reportable disease rule in 1999. However, recorded deaths from CJD, as indicated by ICD-9 cause-of-death code of 046.1 or ICD-10 A81.0 on death certificates from Utah Department of Health's Vital Records, are available as far back as 1980. Death certificate reviews for CJD have been shown to identify greater than or equal to 80% of CJD deaths¹⁵. Between 1980 and 2002, there were a total of 35 probable or confirmed cases of CJD reported or recorded on death certificates in Utah. These cases provide the basis for our knowledge of CJD in Utah.

The median age at death from CJD is 69 years with a range from 30 to 89 years (Figure 1). Since deaths at a young age from non-vCJD are rare, the death of the 30 year old was extensively investigated. It was determined that the patient had sporadic CJD rather than variant. The number of cases reported each year range from a minimum of zero to a maximum of six (Figure 2). The crude annual mortality rate of CJD in Utah is 0.8 cases per million persons (95% CI 0.2, 5.6 per million persons, based on the assumption of a Poisson distribution). This is virtually indistinguishable from the age-adjusted mortality rate of CJD in Utah, which is also 0.8 cases per million persons (standardized using the indirect method, using the US 2000 census population). No significant difference exists between the number of cases in Utah between 1980 and 2002 and what would be expected based on the national average for CJD (expected = 42.7, 95% CI 32.1, 56.7).

Age-specific rates reveal more about the epidemiology of CJD. The mortality rate due to CJD in persons 65 to 85 years is over eight per million persons. This would be expected based on its occurrence primarily in those over 55 years (Figure 1). There is little difference between the distribution of disease in Utah and that seen in the US as a whole^{16,17}.

Neuropathological examination of brain tissue is the only way to definitively diagnose and differentiate between the various human TSEs. It is therefore imperative for surveillance purposes that physicians are aware of the clinical features of CJD and vCJD and to arrange for brain biopsies and or autopsies in all persons suspected of having CJD or any other human TSE¹⁸. In 1997 the National Prion Disease Pathology Surveillance Center (NPDPSC) was organized at Case Western Reserve University in Ohio. They provide free analysis of cerebral spinal fluid, blood, and brain tissue (obtained either at biopsy or autopsy) in order to confirm and identify the precise type of prion disease in a patient. Diagnostic services provided by this center are an essential component of public health's ability to monitor any possible occurrences of vCJD or changes in the epidemiology of sporadic CJD in the United States. Recent reports suggest that BSE may also be linked to cases of sporadic CJD¹⁹, re-emphasizing the importance of an accurate surveillance

system both in Utah and the US. Information about the NPDPSC and its services are available online at www.cjdsurveillance.com. It is essential that all cases of suspect, probable or confirmed CJD be reported to the Utah Department of Health, Office of Epidemiology, (801) 538-6191, and that cause-of-death is clearly indicated on death certificates.

¹ Holman C, Khan AS, Belay ED, Schonberger LB. Creutzfeldt-Jacob disease in the United States 1979-1994: using national mortality data to assess the possible occurrence of variant cases. *Emerg Infect Dis* 1996; 2: 333-7

² Prusiner SB. The Prion Diseases. *Brain Pathol.* 1998 Jul; 8(3):499-513

³ Show-Ling S, Huber MT, Harris DA. A prion protein cycles between the cell surface and an endocytic compartment in cultured neuroblastoma cells. *Biol Chem.* 1993 Jul 25; 268(21): 15922-8

⁴ The UK Creutzfeldt-Jakob Disease Surveillance Unit. <http://www.cjd.ed.ac.uk>

⁵ Brown P, Will RG, Bradley R, Asher DM, Detwiler L. Bovine Spongiform Encephalopathy and Variant Creutzfeldt-Jakob Disease: Background, Evolution and Current Concerns. *Emerg Infect Dis.* 2001; 7(1)

⁶ Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet.* 1996; 347: 921-5

⁷ Probably Variant Creutzfeldt-Jakob Disease in a U.S. Resident – Florida, 2002. *MMWR weekly.* 2002. October 18; 51(41): 927-9

⁸ Prusiner SB. Prion Disease and the BSE Crisis. *Science.* 1997. Oct 10; 278:244-51

⁹ Bruce ME et al. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature.* 1997; 389: 498-501

¹⁰ Brown P. Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease. *BMJ.* 2001. Apr 7; 322: 841-4

¹¹ Spraker TR, et al. Spongiform Encephalopathies in Free-Ranging Mule Deer (*Odocoileus hemionus*) White-tailed deer (*Odocoileus virginianus*) and Rocky Mountain Elk (*Cervus elaphus nelson*) in Northcentral Colorado. *Journal of Wildlife Diseases.* 1997; 33(1): 1-6

¹² Seidl A, Koontz SR, Elder L, Bunch M. Chronic Wasting Disease Overview: Hunter Information. Agricultural and Resource Policy Report. University of Colorado, Department of Agriculture and Resource Economics, Fort Collins, Colorado. June 2003.
<http://dare.agsci.colostate.edu/extension/apr03-04.pdf>

¹³ <http://www.wildlife.utah.gov/news/03-12/cwd2.html>

¹⁴ Fatal Degenerative Neurologic Illnesses in Men Who Participated in Wild Game Feasts – Wisconsin, 2002. *MMWR Weekly.* 2003. Feb 21; 52(07): 125-127.

¹⁵ Davanipour Z, Smoak C, Bohr T, Sobel E, Liwnicz B, Chang S. Death certificates: an efficient source for ascertainment of Creutzfeldt-Jakob disease cases. *Neuroepidemiology.* 1995; 14(1): 1-6

¹⁶ Holman RC, Khan AS, Kent J, Strine TW, Schonberger LB. Epidemiology of Creutzfeldt-Jakob disease in the United States, 1979-1990: analysis of national mortality data. *Neuroepidemiology.* 1995; 14(4): 174-81

¹⁷ Holman RC, Khan AS, Belay ED, Schonberger LB. Creutzfeldt-Jakob Disease in the United States, 1979-1994: Using National Mortality Data to Assess the Possible Occurrence of Variant Cases. *Emerg Infect Dis.* 1996. October-December; 2(4)

¹⁸ Belay ED, Maddox RA, Gambetti P, Schonberger LB. Monitoring the occurrence of emerging forms of Creutzfeldt-Jakob disease in the United States. *Neurology.* 2003; 60: 176-181

¹⁹ Butler D. Prion data suggest BSE link to sporadic CJD. *Nature.* 2002; 420(6915): 450

Fig. 1

